periods. The few studies comparing the efficacy (short- and long-term) of pharmacologic and nonpharmacologic treatments suffer from a variety of conceptual and methodologic difficulties. These include a failure to differentiate patients with panic disorder from those with panic disorder and agoraphobia or those with subtypes of panic disorder, and the heterogeneity of diagnostic criteria, treatment procedures, and measures of clinical success. Thus, our present state of knowledge does not enable us to predict accurately which patients will do best with which treatment(s) or how different treatments might best be integrated.

Patients with PDA should be educated regarding the various treatment options available. The choice of treatment will depend on the training and expertise of the clinician, the availability of specialists, a patient's sense of urgency, available resources, and the preferred type of treatment. If nonpharmacologic treatment is elected, those patients who are not completely relieved of panic attacks after an adequate treatment trial (three months), or who relapse after treatment, should receive appropriate pharmacologic therapy for panic, combined with exposure treatment of phobic avoidance.

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Rational Polydrug Use in Psychiatry

SINGLE-DRUG THERAPY has been the standard for psychopharmacology for the past two decades. This approach is based on clinical studies that excluded multiple drug therapies to decrease variance in the results. There is consensus, however, that 20% to 40% of patients with depression, manic-depressive illness, anxiety disorders (panic disorder and obsessive-compulsive disorder), and schizophrenia either do not respond initially or do not maintain a response to standard single-drug regimens.

Few double-blind placebo-controlled studies have tested polydrug regimens because a large number of patients would be required to achieve statistical significance. We have to rely mainly on case series and reports based on pharmacologic theory or empiric findings. The reasons to use several drugs include a nonresponse to monodrug therapy; the need for imminent clinical remission (from either patient suffering or the financial limitations of waiting for serial therapies to work); the different therapeutic sites of action of multiple agents; additive or multiplicative effects; and the avoidance of side effects. For example, acute mania appears to respond faster, with better patient compliance, and with fewer side effects when a potent benzodiazepine (usually lorazepam or clonazepam) is temporarily added to a regimen of neuroleptic and antimanic agents. In labile manic-depressive illness, prophylaxis with an anticonvulsant (valproate or carbamazepine) or verapamil enhances stability.

Patients with depression that does not abate in three to four weeks with standard antidepressant therapy commonly will have lithium, thyroid, or stimulants added to the regimen. These agents work independently, and several may be used for refractory cases. Some antidepressants produce side effects that can be countered by others. Because the therapeutic effect is additive, two antidepressant heterocyclic reuptake inhibitors can be administered concurrently. This is commonly done when agitation or insomnia occurs with the use of fluoxetine or desipramine by adding trazodone or another sedating agent, such as doxepin or amitriptyline, at night. Although panic disorder often responds to the use of a single agent (such as alprazolam, phenelzine sulfate, or imipramine hydrochloride), subtle fluctuations in anxiety may continue and increase anticipatory anxiety to a disabling degree. Hence, adding the other agent(s), which act through separate mechanisms, is frequently required. A pharmacologic plateau of obsessive-compulsive disorder to the use of clomipramine or fluoxetine may take 12 weeks to occur, with a third of patients not responding. Serotoninergic activity is augmented by adding the other primary drug or buspirone hydrochloride (as much as 100 mg per day), lithium, or fenfluramine hydrochloride.

Schizophrenia is not a unitary disease, but neuroleptics all appear to have equivalent efficacy. Polydrug therapy with older neuroleptics plus clozapine has increasing appeal but few data to support its use. Neuroleptic side effects contribute importantly to noncompliance and morbidity, however. In addition to the well-appreciated use of anticholinergics, the recent understanding of akathisia has led to a low threshold for the use of propranolol hydrochloride (20 to 80 mg per day in divided doses) for this extrapyramidal syndrome of anxiety and motor restlessness. The augmentation of neuroleptic therapy has proved beneficial with the use of carbamazepine, lithium, or benzodiazepines in some schizophrenic patients. Although no specific subgroup is predictably responsive, it is commonly thought that these drugs are relatively more effective in patients with active psychotic symptoms, aggression, or schizoaffective schizophrenia.

The use of several hypnotic agents in a single patient is usually based on their half-life. In selected patients with pronounced difficulty falling and staying asleep, an ultrashort-acting hypnotic (triazolam, for instance) may be beneficial when combined with a longer-acting agent, and the combination has reduced morning sedative side effects.

In these uses of polydrug therapy, each agent is prescribed systematically and for a specific target behavior that can be evaluated for response. This rational use of multiple drugs is therefore valid. It is distinct from older, fixed-dose combination drugs or simplistically adding virtually identical agents without careful reasoning. The search for therapeutic benefit must be tempered by caution about additive side effects such as anticholinergic or hypotensive effects.

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